Protocol Title: A Phase I/II Pilot Study of the Safety of the Adoptive Transfer of Syngeneic Gene-Modified Cytotoxic T Lymphocytes in HIV-Infected Identical Twins

Scientific Abstract: The cell-mediated immune response plays an essential role in the host's defense against viral infection. Studies of cytomegalovirus (CMV) and influenza virus for which small animal models are available have revealed that CD8+ cytotoxic T lymphocytes (CTLs) represent the major component of this cellular immunity. Although optimal animal models for HIV infection await development, evidence that CD8+ CTLs represent the major and earliest immune response to HIV infection is supported by correlative data from HIV-infected patients. The clinical data available suggest that a breakdown of the host cell-mediated immune response may be responsible for progression to symptomatic AIDS. *In vitro* studies have not only confirmed that HIV-specific CD8+ T cells exhibit cytolytic activity toward HIV-infected targets, but have also revealed that CD8+ T cells have the ability to inhibit replication of HIV in lymphocyte cultures. Data supportive of the central role of CD8+ T cells in HIV infection suggest that adoptive transfer of HIV-specific CD8+ T cells may have potential as an immunotherapy for HIV-infected individuals.

Cell Genesys, Inc. has designed universal (HLA-unrestricted) chimeric T cell receptors (URs) that can redirect the antigenic specificity of peripheral blood mononuclear cell (PBMC)-derived CD8+ T cell populations to recognize HIV antigen(s) of choice expressed on the surface of infected cells. Upon binding to viral antigen, these URs initiate T cell activation, resulting in induction of effector functions including cytolysis of the virally-infected cell. The URs developed to date are chimeric receptors composed of antigen recognition and signaling domains. The UR proposed for initial clinical investigation is composed of the extracellular domain of the human CD4 receptor that recognizes the gp120 moiety of HIV env fused to the cytoplasmic domain of zeta, responsible for signal transduction in T cells. Using retroviral-mediated transduction with replication-defective retroviral vectors, we can routinely generate CD8+ T cells stably expressing high levels of HIV-specific URs. The UR+ CD8+ T cell population exhibits highly efficient cytolytic activity against T cells infected with HIV-1. In addition, preliminary findings show inhibition of viral replication of a low passage lymphocytotropic strain of HIV-1.

In a collaborative clinical study between Cell Genesys, Inc. and investigators at the NIH, we will assess the safety and tolerance of adoptive transfer of anti-HIV cytotoxic, syngeneic peripheral blood T lymphocytes containing the CD4-UR into patients with HIV infection. The donors for the CD8+ T cells will be HLA-identical seronegative twins of the HIV-positive patients. The proposed study is an open-label, comparative, sequentially randomized treatment with genetically unmodified or modified *ex vivo*-expanded T lymphocytes. The study is divided into two treatment periods. In the initial period, single doses of genetically unmodified T lymphocytes or single, escalating doses of genetically modifed T lymphocytes will be administered. In the second period, multiple doses of the maximum tolerated cell dose will be administered. By monitoring functional immune status, viral burden, clinical symptoms, organ function, and persistence of circulating gene-modified T lymphocytes, we hope to determine whether this potential therapeutic approach is feasible and safe. This study may form the baseline for future protocols using lymphocytes obtained directly from HIV patients.